UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,003	11/26/2003	Jing Ma	549062000200	9567

30542 7590 07/18/2006

FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,003	MA ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *18 and 37-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17, 19-22, 23, 35, 36 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/6/04; 7/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. Claims 1, 8, 9, 16, 21, 35-37, 40, 43, and 47-49 have been amended, claims 24-34 have been canceled and new claims 50-57 have been added by the Reply of June 5, 2006. The amendments to the claims and the new claims have been considered and entered.

2. Claims 1-23 and 35-57 are all the pending claims for this application.

Election/Restrictions

3. Applicant's election with traverse of Group 2 (Claims 8-17) in the reply filed on June 5, 2006 is acknowledged. The traversal is on the ground(s) that:

a) In paragraph 2 of the Reply, Applicants state that the Claims of Group 2 (Claims 8-17) are an incomplete list and should include linking and generic claims such that the elected claims are 1-17, 19-23 and newly added claims 50-57.

The Examiner reminds Applicant that under MPEP §809, the linking claims are examined with the elected invention, thus claims originally designated as linking claims, Claims 1-7, 19, 20, 35 and 36, have certainly been examined as set forth below. It is further noted that Applicants haven't even considered or mentioned in their Reply that claims 35 and 36 are generic or linking claims to elected Group 2. Thus, for purposes of record and consistency, the Examiner will maintain the linking claim status of Claims 35 and 36.

Applicants have not provided any technical or legal arguments for asserting that Claims 21-23 should be rejoined with Group 2, nor has Applicant even identified why

the Office should consider Claims 21 and 22 as drawn to linking subject matter. The prior art as discussed below, provides examples of chimeric molecules reading on an Flt3 ligand-tumoricidal agent without a linking peptide. A linking peptide does not appear to be a required element of the composition, and Applicants have not provided any evidence to the contrary. Applicants' specification actually teaches chimeric proteins without linker peptides (e.g., SEQ ID NO:28).

The Examiner is even more perplexed that Applicants can assert that all of the chimeric protein embodiments of Claim 23 read on the elected invention for a Flt3 ligand-p230 antibody chimera. In fact, SEQ ID NOS: 24, 26, 28, 30, 32 and 34 comprise antibody (SM5.1 Mab; anti-p230 antibody)-Flex or FL protein constructs, but SEQ ID NOS: 44, 46, 48, 58, 60, 62, 64 are directed to non-elected species for the antibody portion of the molecule. Furthermore, each of the embodiments of Claim 23 is a structurally distinct molecule, which Applicants have not so much as addressed in the Reply.

b) In paragraph 3 of the Reply, Applicants state that searching the claims from the 43 groups would not be extensive and burdensome "because there is not much literature involving Flt-3 ligand", thus "claims of all the identified groups" should be examined. This is not found persuasive because the Examiner's initial search of a commercial database (PubMed) using "Flt3 ligand" as the search term with a date limitation of November 26, 2003 (application filing date) identified 685 relevant hits. Furthermore, and as discussed supra, because Applicant did not distinctly and

specifically point out the supposed errors in the restriction requirement, the requirement is still deemed proper and is therefore made **FINAL IN PART**.

To advance examination of the instantly claimed invention to a chimeric protein, the Examiner has agreed to rejoin Claims 21 and 22 drawn to the linking peptide, and Claim 23 for **only** the embodiments of SEQ ID NOS: 24, 26, 28, 30, 32 and 34.

4. Applicant's election of species to anti-p230 antibody or a biologically active fragment thereof in the reply is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

5. Claims 1-17, 19-22, 23, 35, 36 and 50-57 are all the claims under examination with species to SEQ ID NOS: 24, 26, 28, 30, 32 and 34 and an anti-p230 antibody. Claims 18 and 37-49 are withdrawn as being for non-elected subject matter.

Information Disclosure Statement

6. The U.S. and foreign patent references and the non-patent literature references cited in the IDS' of May 6, 2004 and July 14, 2005 have been considered and made of record.

Drawings

7. The drawings are objected to because Figures 6 and 7; 23 and 24; 31 and 32; and 53, 54 and 55 should be on separate pages.

Correction is required.

Sequence Compliance

8. Pursuant to 37 CFR 1.821, a sequence identifier must be provided for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more nucleotides. The following omissions have been identified in the specification and the sequences do not appear in the Sequence Listing:

a) p. 41, [0163], lines 8 and 9: gca Ctc gag ttt tac Ccg gag Ka ggg aga g and gag ccc aaa tct tgt gac aaa ac

Applicants will need to provide a revised Sequence Listing, a computer readable form of the Sequence Listing and a statement. Please see the attached Notice to Comply Form, for which the Examiner has set a 3-month shortened statutory period for response.

Specification

9. The abstract of the disclosure is objected to because it contains legal phraseology. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The

disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

10. The disclosure is objected to because of the following informalities:

a) p. 5, [0013], line 5: the deposit information for the plasmids is missing;

b) p. 21, [0108], line 5; p. 52, [0193], line 5 and [0195], line 4: $(Gly_4Ser)_3$ should be identified by SEQ ID NO:6 pursuant to 37 CFR 1.821;

c) p. 41, [0163], lines 8 and 9: gca Ctc gag ttt tac Ccg gag Ka ggg aga g and gag ccc aaa tct tgt gac aaa ac should be identified by sequence identifiers pursuant to 37 CFR 1.821;

d) the term "proteinuous" should be amended at each occurrence throughout the specification to – proteinaceous --. This appears to be a typographical error.

Appropriate correction is required.

Claim Objections

11. Claims 16, 21, 22, 23, 52, 56 and 57 are objected to for the following reasons:

a) Claims 16 and 52 are objected to for being drawn to non-elected subject matter.

b) Claims 21 and 56 recite "is" and this appears to be a typographical error. Amending the claims to recite – are -- would overcome this objection.

c) Claims 22 and 57 recite "(Gly4Ser)3" and the term is set forth in the specification as $(G1y_4Ser)_3$. This appears to be a typographical error. Also, pursuant to 37 CFR 1.821, Applicants are required to provide sequence identifiers for any sequence $\geq$4 amino acids, thus the sequence should be identified as SEQ ID NO:6 in the claims.

d) Claim 23 is objected to for being drawn to non-elected subject matter for SEQ ID NOS: 44, 46, 48, 58, 60, 62, 64, 66 and 68.

e) Claim 57 improperly depends from itself and would properly depend from Claim 56.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 6, 8, 9, 21, 36 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1, 8, 9 and 50 are indefinite for the recitation "biologically active" (Claims 1 and 50) and "biological activity" (Claims 8 and 9) because the exact meaning of the phrase is not clear. What biological activity is intended, what cell type should this affect, and how active must a "biologically active" molecule be compared to the native or wild-type Flt3 ligand? The specification teaches that a "derivative or fragment retains at least 50% of its Flt3 stimulating activity" [0095].

b) Claim 6 recites the limitation "the mammalian Flt3 ligand". There is insufficient antecedent basis for this limitation in claim 6, which depends from Claim 1. Amending the claim to depend from Claim 5 would overcome this rejection.

c) Claim 21 recites the limitation "the targeting agent". There is insufficient antecedent basis for this limitation in claim 21, which depends from Claim 1. Amending the claim to recite -- the tumoricidal agent-- would overcome this rejection.

d) Claim 36 is indefinite for the recitation "an effective amount of a chimeric protein" as the product is a kit, and the kit is not limited by an intended use. Therefore, it is unclear what the intended application(s) of the kit reagents are for much less in what application the amount of the chimeric protein is effective for performing.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-8, 11, 14-17, 19-22, 35, 36 and 50-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-7, 14-17, 19-22, 35, 36 and 50-57 are drawn to a chimeric protein comprising an Flt3 ligand and a tumoricidal agent where any Flt3 ligand is encompassed by the claims. Claim 8 is drawn to the Flt3 ligand having at least 40% sequence identity with the amino acid stretch spanning 100 amino acid residues for the sequence of SEQ ID NO:2, and Claim 11 is drawn to the chimeric protein where the Flt3 ligand has at least 80% sequence identity with SEQ ID NO:2.

The specification defines the term "Flt3 ligand" as a genus of polypeptides that bind and induce signaling through the Flt3 receptor found of progenitor cells [0090-0091] yet the only embodiment of an Flt3 ligand disclosed in the specification has SEQ ID NO:2 or an amino acid sequence comprising amino acid residues 28-128, 28-160 or 28-180 of SEQ ID NO:2 [0096]. The specification discloses a cloned extracellular domain of Flt3 ligand (Flex) [Example 1], chimeric SM5-1 antibody and humanized forms [Example 2], and construction of SM5-1/Flt3 ligand chimeric molecules of SEQ ID NOS: 24, 26, 28, 30, 32 and 34 [Example 4]. The are no examples of chimeric molecules comprising a Flt3 ligand (full or Flex forms) having at least 40% or 80% sequence identity with SEQ ID NO:2 much less any other nucleotide or amino acid sequence for any other Flt3 ligand.

The specification does not provide sufficient written description as to the structural features of the claimed genus of Flt3 ligand nucleic acids and encoded polypeptides and the correlation between the chemical structure and function of the genus of Flt3 ligand nucleic acids or amino acids, such as structural domains or motifs that are essential and distinguish members of the genus from those excluded. Additionally, the specification does not disclose a single species with less than 100% sequence identity for the Flt3 ligand or the soluble, extracellular domain, Flex, of SEQ ID NO:2.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species

to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the genus. " See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

It has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities. Based on the instant disclosure one of skill in the art would not know which sequences are essential, which sequences are non-essential and what particular sequence lengths identify essential sequences for identifying a Flt3 ligand nucleic acid sequence or amino acid sequence encompassed by the claimed specificity. For

example, there is insufficient guidance based on the reliance of disclosure of SEQ ID NO:2 to direct a person of skill in the art to select or to predict particular sequences as essential for identifying Flt3 ligand amino acids encompassed by the claimed specificities. Mere idea of function is insufficient for written description; isolation and characterization at a minimum are required.

Scholnick et al (Trends in Biotechnology, 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based on sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to function of the structurally related protein (see in particular "Abstract" and Box 2).

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance on the activity of the Flt3 ligand polypeptides encoded by SEQ ID NO:2, disclosed in the specification as-filed does not appear to provide sufficient written description for the genus of amino acid sequences or nucleic acid sequences encompassed by the claimed specificities in view of the above evidence, which indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.

For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case, applicant has not even disclosed a single species encompassed by the a highly variant protein moiety of Claim 8 comprising a sequence having at least 40% sequence identity with SEQ ID NO:2, nor is there disclosure of the common attributes or features (i.e., structural domains) that are essential for activity or those which are non-essential. See, e.g., Eli Lilly. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the

'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only an isolated Flt3 ligand of amino acid sequences comprising SEQ ID NO: 2, but not the full breadth of claims 1-8, 11, 14-17, 19-22, 35, 36, 50-56 meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

14. Claims 1-8, 11, 14-17, 19-23, 35, 36 and 50-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making

and using a) chimeric protein comprising the Flt3 ligand (FL) or the extracellular, soluble domain (Flex) of SEQ ID NO:2 linked via peptide linker or unlinked to an apoptosis-inducing tumoricidal agent such as an antibody or fragment thereof, which retains antigen binding activity for inhibiting proliferation or reducing tumor cell viability such as anti-p230 antibody (SM5-1 Mab), or b) chimeric proteins of SEQ ID NOS: 28 (FL/Fc/huSMFv) and 34 (FL/Fc/chSMFv), does not reasonably provide enablement for making or using a chimeric protein comprising just any known or yet to be discovered Flt3 ligand moiety fused to just any tumoricidal agent moiety much less a chimeric protein where the biological activity for each of the moieties is retained or SEQ ID NOS: 24, 26, 30 and 32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 1-8, 11, 14-17, 19-23, 35, 36, 50-56 are drawn to a chimeric proteins comprising an Flt3 ligand or biologically active fragment and a protein based tumoricidal agent such as antibody, specifically an anti-p230 antibody or fragments thereof, which

inhibits tumor cell proliferation or reduced viability such as inducing apoptosis, the Ftl3 ligand sitmulates hematopoietic or progenitor cell proliferation or myeloid precursor cells, monocytic cells, macrophages, B-cells, dendritic cells or NK cells, the Ftl3 ligand is mammalian or human, or soluble, the Ftl3 ligand is located at the 5' or 3' of the protein, the two moieties are connected by a peptide linker of $(Gly_4Ser)_3$, the Flt3 ligand binds to an antibody binding to SEQ ID NO:2, the antibody being human or humanized, and pharmaceutical compositions and kits comprising the chimeric protein. Claim 23 is drawn to SM5.1/Flt3 ligand chimeric protein embodiments for SEQ ID NOS: 24, 26, 30 and 32.

The interpretation of the specification is discussed under section 13, supra.

a) The specification is not enabled for making or using just any Flt3 ligand or an FLt3 ligand having any percent identity with SEQ ID NO:2.

The claims are not commensurate in scope with the enablement provided in the specification because any discovered or yet to be discovered Flt3 ligand is encompassed within the scope. And for the Flt3 ligand comprising SEQ ID NO:2, the specification does not disclose any species for Flt3 ligand molecules having at least 40% or 80% sequence identity with SEQ ID NO:2. The specification does not support the broad scope of the claims which encompass all modifications to the amino acid sequence because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed Flt 3ligand in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).
Further protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, see the discussion of Burgess and Lazar under section 13, supra. Additionally, other references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. For example, replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its

receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

b) The specification is not enabled for using SEQ ID NOS: 24, 26, 30 and 32 which comprise only the VH domain of SM5.1 Mab.

Claim 23 is drawn to SM5.1/Flt3 ligand chimeric proteins of SEQ ID NOS: 24 (huSMVH/Fc/FL), 26 (huSMVH/Fc/Link/FL), 30 (chSMVH/Fc/FL), and 32 (chSMVH/Fc/Link/FL). Each of the embodiments comprises only the VH domain of SM5.1 Mab. The claim is not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 79:1979). Rudikoff et al. teach that the

alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fragments of antibodies as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody, have the required binding function. The specification provides no direction or guidance regarding how to use chimeric polypeptides having binding specificity to the p230 protein as broadly defined by the claims or what combination of antibody domains VH, VL, CH1, CH2, CH3, Fc, etc would confer this specific binding to p230 protein. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the broadly claimed invention, the lack of predictability in the art as evidenced by Burgess, Lazar, Schwartz, Lin and Rudikoff, and lack of guidance in the specification with regard to producing and/or using the myriad chimeric FLT3 ligand/ SM5.1 antibody molecules, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 1-7, 19, and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wu et al. (Molec. Ther. 3:368-374 (Mar 2001); hereinafter referred to as "Wu") as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000); hereinafter referred to as "Antonysamy").

Claims 1-7, 19, and 21 are drawn to a chimeric proteins comprising an Flt3 ligand or biologically active fragment and a protein based tumoricidal agent which inhibits tumor cell proliferation or reduced viability such as inducing apoptosis, the Ftl3 ligand sitmulates hematopoietic or progenitor cell proliferation or myeloid precursor cells, monocytic cells, macrophages, B-cells, dendritic cells or NK cells, the Ftl3 ligand is mammalian or human, or soluble, the Ftl3 ligand is located at the 5' of the protein, and the two moieties are connected by a peptide linker.

Wu discloses a fusion protein comprising the soluble form of the human Flt3 ligand (Flex) at the 5' end and the human TNF-related apoptosis-inducing ligand (TRAIL) at the 3' end with or without a peptide linker comprising an isoleucine zipper linking the two moieties (hFlex-zipper-TRAIL (FETZ) or FET, respectively) (p.369, Col. 1, ¶3; Figure 1); TRAIL induces apoptosis in many human tumor cell lines (p. 368, Col. 2, ¶) and is a ligand toxic to tumors (p. 369, Col. 1 ¶3); hFLex is a hematopoietic growth factor that stimulates proliferation and differentiation of hematopoietic progenitors (p. 369, Col. 1, ¶3) and expansion of dendritic cell population (p. 369, Col. 1, ¶3; Figure 7); both FETZ and FET tested on MDA-231 human mammary carcinoma cell line induced cell death as measured by cell viability (p. 372, Col. 1, ¶1-3; Figures 5-7). The ability of Flt3 ligand to stimulate proliferation of myeloid precursor cells, monocytic cells,

macrophages (p. 89, Col. 1, ¶4 and Col. 2, ¶3), B-cells (p. 89, Col. 2, ¶4; p. 90, Col. 2, ¶2), dendritic cells (p. 90, Col. 2, ¶4- p. 92, Col. 2, ¶1) and NK cells (p. 90, Col. 2, ¶3) was already known in the art as evidenced by Antonysamy.

Applicant is reminded that because the claims recite "comprising" language, any chimeric protein comprising a Flt3 ligand moiety and an apoptosis-inducing tumoricidal moiety such as TRAIL, is encompassed by the claims, and therefore anticipated by Wu.

17. Claims 1, 3-5, 7, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hung et al. (Cancer Research. 61:1080-1088 (February 1, 2001); hereinafter referred to as "Hung") as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000); hereinafter referred to as "Antonysamy").

The interpretation of Claims 1, 3-5, 7 and 19 is discussed supra.

Hung discloses a recombinant chimera of the extracellular domain of Flt3-ligand (FL) linked to human papillomavirus-16 E7 (Abstract); Flt3-ligand induces a growth-stimulatory effect on DC precursors (p. 1080, Col. 2,. ¶2); HPV-16 oncogenic protein E7 is expressed in most HPV-containing cervical cancers (p. 1080, Col. 2, ¶3); vaccine or immunotherapies targeting E7 protein may provide treatments for HPV-associated cervical cancers (p. 1080, Col. 2, ¶3); the signal peptide and extracellular domain of mouse FL was prepared by DNA primer amplification with a mouse FL DNA template, sfHAV-EO419 (p. 1081, Col. 1, ¶1); vaccination of mice with chimeric HL-E7 enhances protection of mice against the growth of TC-1 tumors (p. 1083, Col. 1-2; Figures 4-6); linkage of the FL gene to an antigen gene may greatly enhance the potency of DNA

vaccines and can potentially be applied to other cancer systems with known tumor-specific antigens (p. 1087, Col. 1, ¶6). See the interpretation of Antonysamy with respect to the Flt3 ligand and its proliferation stimulatory properties discussed supra.

Applicant is reminded that because the claims recite "comprising" language, any tumoricidal agent with the ability to reduce tumor cell viability is encompassed by the claims, and therefore anticipated by Hung.

18. Claims 1-5 and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wang et al. (Chinese Micro. & Immunol. J. 20(5):397-401 (2000); hereinafter referred to as "Wang") as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000); hereinafter referred to as "Antonysamy").

The interpretation of Claims 1-5 is discussed supra. Claim 20 is drawn to the Ftl3 ligand being located at the C-terminus of the protein.

Wang discloses a chimeric protein comprising HSV thymidine kinase (TK) and Flt3 ligand (FL) and expressed in MCF-7 mammary tumor cell line. Apoptosis of the cells was measured by EM and flow cytometry. Wang discloses using the MCF/TK-FL cells for tumor therapy. See the interpretation of Antonysamy with respect to the Flt3 ligand and its proliferation stimulatory properties discussed supra.

Applicant is reminded that because the claims recite "comprising" language, any tumoricidal agent with the ability to reduce tumor cell viability is encompassed by the claims, and therefore anticipated by Hung.

19. Claims 1-6, 14, 15, 20, 35, 50, 51, and 55 are rejected under 35 U.S.C. § 102(b) as being anticipated by Krieg et al. (USPN 6,218,371; published April 17, 2001; filed April 2, 1999); hereinafter referred to as "Krieg") as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000); hereinafter referred to as "Antonysamy").

The interpretation of Claims 1-6 and 20 are discussed supra. Claims 14 and 15 are drawn to an antibody and antibody fragments, Claim 35 is drawn to a pharmaceutical composition comprising the chimeric protein and a pharmaceutically acceptable carrier, Claims 50 and 51 are drawn to a chimeric protein comprising the Flt3 ligand and an antibody or antibody fragment which inhibits proliferation or reduced viability of tumor cells, and Claim is drawn to the Flt3 ligand being located at the C-terminus.

Kreig discloses an antigen-cytokine fusion protein (Col. 3, line 22-23) where the idiotype of a secreted immunoglobulin serves as a highly specific tumor associated antigen. The "idiotype" comprises a collection of V-region determinants specific to a specific antibody or a limited set of antibodies. In one embodiment, the immunopotentiating cytokine is a protein (a fusion protein) consisting of a specific antigen idiotype secreted by a lymphoma fused to the immunopotentiating cytokine (Col. 9, lines 31-40); an immunopotentiating cytokine is human Flt-3 ligand (Col. 8, line 63- Col. 9, line 1); a idiotype (Id) of the 38C13 surface IgM serves as a highly specific tumor-associated antigen (Example 1); pharmaceutical composition comprising the fusion protein with a pharmaceutically-acceptable carrier (Col. 31, lines 13-33).

20. Claims 1-5, 14, 15, 17, 19, 20, 35, 36, 50, 51 and 53-55 are rejected under 35 U.S.C. § 102(e) as being anticipated by Tang et al. (USPN 6,783,969; published August 31, 2004; filed March 5, 2001); hereinafter referred to as "Tang").

The interpretation of Claims 1-6, 14, 15, 19, 20, 35, 50, 51 and 55 is discussed supra. Claims 17 and 53 are drawn to a human or humanized antibody, Claim 36 is drawn to a kit comprising the chimeric protein with instructions, and Claims 54 and 55 are drawn to the Flt3 ligand being located at the N- or C-terminus of the chimeric protein.

Tang discloses a chimeric protein or fusion protein where the polypeptide can be fused to the N-terminus or C-terminus, or to the middle (Col. 26, lines 45-60); a polypeptide operably linked to the extracellular domain of a second protein (Col. 26, lines 61-63); the fusion protein is an immunoglobulin fusion protein in which the polypeptide sequences comprise one or more domains fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins can be incorporated into pharmaceutical compositions; the immunoglobulin fusion proteins can be used to affect the bioavailability of a cognate ligand. Inhibition of the ligand/protein interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, e.g., cancer as well as modulating (e.g., promoting or inhibiting) cell survival (Col. 27, lines 1-20); a polypeptide may exhibit stem cell growth factor activity and be involved in the proliferation, differentiation and survival of pluripotent and totipotent stem cells including primordial germ cells, embryonic stem cells, hematopoietic stem cells and/or germ line stem cells (Col. 33, lines 21-26) and

include Flt-3 ligand (Flt-3L) (Col. 33, line 48); the term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen-binding site that specifically binds (immunoreacts with) an antigen. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, F_{ab}, $F_{ab'}$, and $F_{(ab')2}$ fragments; human antibodies (Col. 59, lines 25-41); humanized antibodies (Col. 63, line 36- Col. 65, line 45); kits accompanied by instructions for administration (Col. 59, lines 14-23).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. Claims 1-7, 10, 12, 13, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (Molec. Ther. 3:368-374 (Mar 2001); hereinafter referred to

as "Wu") in view of Lynch et al. (US20030113341; published June 19, 2003; filed September 11, 2002; hereinafter referred to as "Lynch").

The interpretation of Claims 1-7, 19 and 21 are discussed supra. Claims 10, 12 and 13 are drawn to the Flt3 ligand comprising SEQ ID NO:2, amino acids 28-128 of SEQ ID NO:2, amino acids 28-160 of SEQ ID NO:2.

The interpretation of Wu is discussed supra. Wu does not disclose the Flt3 ligand comprising SEQ ID NO:2, amino acids 28-128, 28-160 or 28-180 of SEQ ID NO:2. Lynch rectifies this deficiency in its disclosure.

Lynch discloses that the Flt3-ligand ("flt3-ligand," "flt3-L," "Flt3-L") is known to affect hematopoietic stem and progenitor cells, and can potently stimulate the generation of downstream or intermediate, cells such as myeloid precursor cells, monocytic cells, macrophages, B cells, and dendritic cells from CD34+ bone marrow progenitors and stem cells [0007]; a combination therapy comprising the flt3-ligand and one or more therapeutic reagents [0008] including antibodies to 4-1BB [0012]; the term "flt3-L" encompasses proteins having the amino acid sequence 1 to 235 of SEQ ID NO:2, as well as those proteins having a high degree of similarity or a high degree of identity with the amino acid sequence 1 to 235 of SEQ ID NO:2, and which are biologically active and soluble, or truncated proteins which comprise primarily the extracellular portion of the protein, retain biological activity and are capable of being secreted. Specific examples of such soluble proteins are those comprising the sequence of amino acids 28-160 of SEQ ID NO:2 [0019]; soluble mammalian flt3-L proteins comprise amino acids 28 through 182 of SEQ ID NO:2 [0024]; Flt3-ligand

comprising amino acids 28 to Xaa of SEQ ID NO:2, wherein Xaa is an amino acid from 160 to 235 (claim 12); antibodies reactive with 4-1BB, both of which are T-cell co-activation factors, can be administered in combination with flt3-L to dramatically enhance immune responses and the surprising synergy in the combination therapies to dramatically enhance anti-tumor immune responses suggests that stimulating more than one mechanism or more than one cell population is a promising approach to cancer treatment [0050];

It would have been *prima facie* obvious to have produced the instantly claimed chimeric protein and pharmaceutical compositions in view of Wu and Lynch.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed chimeric protein in view of Wu and Lynch because Wu discloses the advantages of using hFlex-linker-TRAIL proteins is that it results in substantial tumor regression or tumor ablation and the expansion of DC population. Wu discloses that the fusion protein is:

> "an illustration of a new concept, which provides a rationale for the use of a ligand toxic to tumor cells fused with an adjuvant such as cytokine or Flt3L to achieve dual function in cancer therapy." (p. 369, Col. 1, ¶3 to Col. 2, ¶1).

Wu discloses fusion proteins where hFlex has an N-terminal signal peptide sequence which may be sufficient to allow secretion of the fusion protein (Figure 1). Wu teaches that a chimeric protein comprising a full length soluble Flt3L linked to the tumoricidal agent, TRAIL, was expressed by host cells with the individual moieties remaining biologically active, thus providing the added advantage of there being a single, dual-

acting recombinant molecule for administration purposes (p. 373, Col. 2, ¶ 2). Lynch discloses an Flt3L protein with the native signal peptide, such that the mammalian flt3-L comprises 1 through 182 of SEQ ID NO:2 (i.e., SEQ ID NO:2 of Lynch) [0024]. Lynch discloses soluble mammalian flt3-L proteins comprise amino acids 28 through 182 of SEQ ID NO:2 (of Lynch) and truncated soluble flt3-L proteins comprising less than the entire extracellular domain such as amino acids 28-160 of SEQ ID NO:2 [0024] and combining these soluble forms with other tumoricidal therapies, e.g., antibodies, to provide synergistic cancer therapies. One skilled in the art could have readily cloned the Flt3L fragments disclosed in Lynch to create a fusion protein with the Flt3L fragment being N- or C-terminal to the tumoricidal agent according to Wu because the reagents and molecular biological technology for cloning truncated forms of soluble Flt3L were available at the time of the invention. Also, with truncated soluble forms of Flt3L being biologically active according to Lynch, one of skill in the art would have been motivated to have and could have readily cloned such molecules into the C-terminal portion of the fusion protein where a signal peptide was not required for secretion of the fusion protein. Additionally since Wu discloses a full-length cDNA for human TRAIL, one could have created a TRAIL-linker-Flt3-L protein using the native signal peptide of TRAIL and any of the truncated soluble FLt3L fragments. The combined reference disclosures of Wu and Lynch provide more than sufficient motivation to have created the instantly claimed fusion protein, thus the claimed invention was obvious at the time of the invention.

22. Claims 1, 16, 50 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (USPN 6,783,969; published August 31, 2004; filed March 5, 2001); hereinafter referred to as "Tang") as applied to claims 1 and 50 above, and further in view of Trefzer et al. (Arch Dermatol. Res. 292:583-589 (2000); hereinafter referred to as "Trefzer").

The interpretation of Claims 1 and 50 are discussed supra. Claims 16 and 52 are drawn to the tumoricidal agent being an anti-p230 antibody. The specification defines SM5-1 as an anti-p230 antibody (p. 17, [0099]).

The interpretation of Tang is discussed supra. Tang does not disclose SM5-1 antibody. Trefezer rectifies this deficiency in its disclosure.

Trefezer discloses the SM5-1 antibody having been raised in mice first given a human melanoma cell line SMMUneg followed by the human melanoma cell line SMMUpos obtained from a metastatic lesion of the same patient. The SM5-1 antibody was highly sensitive for staining both primary and melanocytic lesions.

It would have been *prima facie* obvious to have produced the instantly claimed chimeric protein comprising the SM5-1 antibody as a tumoricidal agent in view of Tang and Trefezer.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed chimeric protein in view of Tang and Trefezer because Tang discloses therapeutic fusion proteins having tumoricidal activity comprising antibodies and Flt3 ligand. Given that the SM5-1 antibody is more highly sensitive in

detecting a melanocytic lesion compared with other art-recognized antibodies, one skilled in the art could have readily cloned the SM5-1 antibody from its hybridoma based on the disclosure of Tang into a chimeric molecule encoding the SM5-1 (anti-p230 antibody) and the Flt3 ligand to obtain a tumor specific chimeric protein. Thus the claims were prima facie obvious over Tang and Trefezer at the time of the invention.

23. Claims 1, 22, 50 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (Molec. Ther. 3:368-374 (Mar 2001); hereinafter referred to as "Wu") as applied to claim 1 above, and Tang et al. (USPN 6,783,969; published August 31, 2004; filed March 5, 2001); hereinafter referred to as "Tang") as applied to claim 50 above, and further in view of Sandee et al. (BMC Biotechnology 2:16-23 (2002); hereinafter referred to as "Sandee").

The interpretation of claims 1 and 50 is discussed supra. Claims 22 and 57 are drawn to a linker peptide comprising $(Gly_4Ser)_3$.

The interpretation of Wu and Tang are discussed supra. Neither Wu nor Tang disclose a peptide linker comprising $(Gly_4Ser)_3$. Sandee rectifies this deficiency in its disclosure.

Sandee discloses an anti-hepatocellular carcinoma scFV where the VH and VL are linked by $(Gly_4Ser)_3$. Sandee discloses that the fusion protein retains the original antigen binding site, and represents valuable molecules for targeted delivery of drugs, toxins to tumor site, and that the molecules can be further manipulated by genetic engineering to form anti-tumor fusion proteins with additional effector functions (p. 17,

Col. 2, ¶1). Sandee teaches that the $(Gly_4Ser)_3$ linker is flexible and improves stability of the domains, a variety of linkers are available but "the most widely used linker designs have stretches consisting primarily of glycine and serine residues. Hydrophilic properties of serine allow hydrogen bonding to the solvent and glycines provide the necessary flexibility." (p. 19, Col. 2 to p. 20, Col. 1).

It would have been *prima facie* obvious to have produced the instantly claimed chimeric protein comprising the $(Gly_4Ser)_3$ linker in view of Wu and Sandee or Tang and Sandee.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed chimeric protein in view of Wu and Sandee or Tang and Sandee, because as Sandee discloses several linkers were already known and the properties that each conferred on the fusion or chimeric protein had its advantages or problems. Sandee discloses that $(Gly_4Ser)_3$ linker was widely known and available for producing improved chimeric molecules, thus one skilled in the art would have been motivated and been reasonable assured of success in inserting the $(Gly_4Ser)_3$ linker into a chimeric protein of Wu and/or Tang with expectation that the molecule would retain its biological activity. Thus the claims were *prima facie* obvious in view of Wu and Sandee or Tang and Sandee at the time of the invention.

24. Claims 1 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang and Lynch as applied to claim 1 above, and further in view of Trefzer.

The interpretation of Claim I is discussed supra. Claim 23 is drawn to the fusion proteins of SEQ ID NOS: 28 (FL/Fc/huSMFv) and 34 (FL/Fc/chSMFv). The specification defines SM5-1 as an anti-p230 monoclonal antibody (p. 17, [0099]) and that "SM5-1 (IgG1, K) hybridoma cells" are "(deposited at ATCC having ATCC Designation No. HB-12588)" (p. 42, [0164]).

The interpretation of Tang and Lynch is discussed supra. Neither Tang nor Lynch disclose a Flt-3 ligand/antibody chimeric protein where the antibody comprises fragments of SM5.1 (anti-p230 Mab). Trefzer discloses the SM5-1 hybridoma and antibody as discussed supra, and rectifies the deficiencies of Tang and Lynch.

It would have been *prima facie* obvious to have produced the instantly claimed chimeric SM5-1/Flt3 ligand protein comprising SEQ ID NOS: 28 (FL/Fc/huSMFv) and 34 (FL/Fc/chSMFv) in view of Tang, Lynch and Trefzer.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed chimeric protein in view of Tang, Lynch and Trefzer. Tang discloses fusion proteins comprising antibody fragments (i.e., single chain Fv) fused to or administered in combination with immunostimulatory cytokines such as Flt3 ligand and the advantages of such proteins in modulating cancer cell survival, Lynch discloses full length sequence for Flt-3 ligand comprising amino acids 1-235 corresponding to SEQ ID NO:2, and Trefzer discloses the SM5-1 hybridoma and properties of the Mab in being highly selective over other mAbs in recognizing the p230 protein in melanocytic lesions. "The discovery of a previously unappreciated property of a prior art

composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997). Trefzer discloses the SM5-1 Mab, and one skilled in the art would envisage that the Fc and SMVH regions comprising the molecule of SEQ ID NOS: 28 and 34, would have been inherent to the antibody of Trefzer. The molecular biological tools for producing antibody based recombinant fusion proteins were taught by Tang at the time of the invention. Further in view of Tang's disclosure that treating cancers through immunopotentiating reagents such Flt-3 ligand was improved and that the materials and reagents for the SM5-1 Mab of Trefzer and the cloned Flt3 ligand of Lynch were available for engineering the proteins into recombinant fusion products, one skilled in the art would have been motivated to have produced and could have been reasonably assured of success in producing the instantly claimed fusion proteins in order to obtain bispecific molecules with immunopotentiating properties and tumor antigen targeted specificity in combining the disclosures of Tang, Lynch and Trefzer. Thus the claims were prima facie obvious at the time of the invention in view Tang, Lynch and Trefzer.

Conclusion

25. Claim 9 appears to be free of the prior art.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10/723,003	Applicant(s) Ma et al.	
	Examiner Lynn Bristol	Art Unit 1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

Pursuant to 37 CFR 1.821, a sequence identifier must be provided for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more nucleotides. The following omissions have been identified in the specification:

a) p. 41, [0163], lines 8 and 9: gca Ctc gag ttt tac Ccg gag Ka ggg aga g and gag ccc aaa tct tgt gac aaa ac